



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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# Isosporiasis (Cystoisosporiasis) (Last updated February 8, 2019; last reviewed February 8, 2019)

## Panel's Recommendations

- I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of isosporiasis (cystoisosporiasis)?
  - Careful hand washing and thorough washing of fruits and vegetables are recommended to prevent exposure. Travelers to isosporiasis-endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables (**expert opinion**).
- II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat isosporiasis (cystoisosporiasis)?
  - Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in children with HIV infection (**strong, high**).
  - Supportive care, including replenishment of fluids and electrolytes, should be provided (**expert opinion**).
- III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of isosporiasis (cystoisosporiasis)?
  - Antiretroviral therapy (ART) administered to children with HIV infection to reverse or prevent severe immunodeficiency may be effective in preventing recurrence of isosporiasis (**weak, very low**).
  - In children with severe immunosuppression, treatment of isosporiasis should be followed by secondary prophylaxis with TMP-SMX (**strong, high**).
- IV. In children with HIV infection receiving secondary prophylaxis for isosporiasis (cystoisosporiasis), when can secondary prophylaxis be safely discontinued?
  - Clinicians may consider discontinuing secondary prophylaxis in patients without evidence of active *Isospora* infection who have sustained improvement in immunologic status (CDC immunologic category 1 or 2) for >6 months in response to ART (**weak, very low**).

## Rating System

Strength of Recommendation: Strong; Weak

Quality of Evidence: High; Moderate; Low; or Very Low

## Introduction/Overview

### Epidemiology

*Isospora belli* (*Cystoisospora belli*) is an intestinal coccidian parasite in the phylum Apicomplexa. It was first linked with human disease in 1915 and is believed to infect only humans.<sup>1</sup> Isosporiasis, also known as cystoisosporiasis, occurs worldwide but is more prevalent in tropical and subtropical regions; it has been reported as an etiologic agent of traveler's diarrhea.<sup>2-4</sup> Before the availability of combination antiretroviral therapy (ART), the prevalence of isosporiasis among adults with AIDS was reported to be 15% in Haiti but <0.2% in the United States.<sup>1,5</sup> In several more recent studies from India, *Isospora* was detected in a range of 16% to 47% of patients with HIV with diarrhea.<sup>6-9</sup> In two of the studies, 50% and 81.8% of individuals with *Isospora* infection had CD4 T lymphocyte (CD4) counts <200 cells/mm<sup>3</sup>.<sup>8,9</sup>

Infected individuals pass noninfective, unsporulated (immature) oocysts in their stool. The oocysts must sporulate (mature) outside the host, in favorable environmental conditions, to become infective.<sup>1,4</sup> Therefore, direct person-to-person transmission of *Isospora* is unlikely. Infection results from ingestion of sporulated oocysts, such as in contaminated food or water. In the proximal small intestine, the ingested oocysts release sporozoites that invade the intestinal epithelial cells. Asexual and sexual stages of the parasite are found in the intestine, and unsporulated oocysts are shed in stool.<sup>1,10</sup>

## Clinical Manifestations

Based on limited data, the incubation period averages approximately 1 week but may range from several days to  $\geq 2$  weeks; symptom onset may be acute or insidious.<sup>1,2,4,5</sup> The most common symptom is watery (non-bloody) diarrhea, which can be profuse and result in dehydration, weight loss, and malabsorption. Affected people also can have crampy abdominal pain, flatulence, nausea, vomiting, anorexia, and low-grade fever. Biliary disease (cholecystitis/choangiopathy) and reactive arthritis also have been reported.<sup>11,12</sup> Whereas immunocompetent hosts typically have self-limited infection, chronic and debilitating diarrhea is common in patients with uncontrolled HIV.

## Diagnosis

Isosporiasis is diagnosed by identifying *I. belli* oocysts in stool (or duodenal aspirates using the Entero-Test) or developmental stages of the parasite in biopsy specimens (e.g., of the small intestine). *I. belli* oocysts are relatively large (23–33  $\mu\text{m}$  long by 10–19  $\mu\text{m}$  wide) but may be difficult to find. Oocysts may be shed in low numbers even by individuals who have severe diarrhea, which underscores the value of repeated stool examinations and use of methods that concentrate and highlight the parasite. Although staining is frequently variable, the organism can be identified with use of a modified acid-fast stain, staining bright red on a green background.<sup>5,10</sup> The organism also autofluoresces when viewed by ultraviolet fluorescence microscopy.<sup>1</sup> Blunting and clubbing of villi and hypertrophied crypts can be seen in small bowel biopsy specimens. There also may be an increase in lymphocytes, plasma cells, and eosinophils in the lamina propria.<sup>10</sup> Peripheral eosinophilia occurs in up to half of patients. Serologic tests are not available. Polymerase chain reaction is a promising diagnostic tool but is not yet commercially available in the United States.<sup>13</sup>

## Prevention Recommendations

### *Preventing Exposure*

Avoiding food or water that might be contaminated with stool may help prevent infection. Careful hand washing and thorough washing of fruits and vegetables are recommended. Hands should be washed with soap and warm water after using the toilet or changing diapers and before handling food.

### *Preventing First Episode of Disease*

There are no U.S. recommendations for primary prophylaxis of isosporiasis. Prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX, 160 mg and 800 mg of TMP and SMX, respectively) was effective in preventing isosporiasis in adults with World Health Organization stage 2 or 3 HIV infection in Cote d'Ivoire.<sup>14</sup> In addition, in an observational study, the incidence of isosporiasis decreased after widespread availability of ART, except among persons with CD4 counts  $< 50$  cells/mm<sup>3</sup>.<sup>15</sup>

Although studies in children are lacking, the relationship between severe immunosuppression and disease in adults suggests that initiating ART in children with HIV before they become severely immunodeficient may reduce the incidence of isosporiasis.

### *Discontinuing Primary Prophylaxis*

Not applicable.

## Treatment Recommendations

### *Treating Disease*

TMP-SMX is the recommended treatment for isosporiasis. Three studies performed among adults with HIV in Haiti who were not receiving ART have demonstrated the effectiveness of various TMP-SMX regimens.<sup>5,16,17</sup> In the first study, TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) was administered 4 times daily for 10 days and then twice daily for 3 weeks. In all 15 patients, diarrhea and

abdominal pain resolved within 2 days of starting treatment, but 7 patients had recurrent symptoms within a mean of 8 +/- 5.8 weeks following completion of therapy.<sup>5</sup> In the second study, TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) was administered 4 times daily for 10 days; participants were then randomized to 1 of 3 secondary prophylaxis arms. At the completion of the initial 10 days of TMP-SMX therapy, all 32 participants had resolution of diarrhea and abdominal pain and negative stool samples.<sup>16</sup> In the third study, participants were randomized to receive either TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) twice daily for 7 days. TMP-SMX treatment was associated with cessation of diarrhea in all 10 patients and negative results on stool examination at day 7 in 9 of the 10 participants, while ciprofloxacin was associated with resolution of diarrhea in 10 of 12 participants and negative stool examinations in 9 of the 12 participants.<sup>17</sup> On the basis of these studies in adults, the recommended treatment for children with HIV is TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Daily pyrimethamine (50–75 mg in adults), with folinic acid (10–25 mg/day) to prevent myelosuppression, may be an effective therapy and is the traditional treatment alternative for patients who are intolerant of TMP-SMX.<sup>18</sup> Other potential agents to consider for TMP-SMX-intolerant patients include ciprofloxacin or nitazoxanide. Data from a randomized, controlled clinical trial described above<sup>17</sup> show that ciprofloxacin is less effective than TMP-SMX; limited data are available about use of nitazoxanide for treatment of isosporiasis.<sup>19,20</sup>

As with all cases of diarrhea regardless of the cause, supportive care, including replenishment of fluids and electrolytes, is essential.

### ***Monitoring and Adverse Events (Including IRIS)***

Immune reconstitution inflammatory syndrome has not been reported in association with treatment of isosporiasis. In general, recommended treatment regimens are well-tolerated.

### ***Managing Treatment Failure***

If symptoms worsen or persist, the frequency of the TMP-SMX dose may be increased to 3 to 4 times daily and/or the duration of treatment lengthened up to 3 to 4 weeks.<sup>5,21</sup> Alternative agents (ciprofloxacin or nitazoxanide) can also be tried. Limited data regarding treatment outcomes are available for albendazole,<sup>22-24</sup> doxycycline,<sup>25</sup> roxithromycin,<sup>26</sup> and spiramycin.<sup>27</sup>

### ***Secondary Prevention***

The relationship between the use of ART and recovery from isosporiasis remains unknown. However, because the incidence of isosporiasis has been reported to be higher in more severely immunosuppressed patients,<sup>15</sup> it seems reasonable that initiation of ART in children with isosporiasis who are not already receiving ART to attempt to improve immunologic status may be effective in decreasing the risk of relapse.

Following treatment of an acute episode of isosporiasis, secondary prophylaxis should be administered to patients with severe immunosuppression (Centers for Disease Control and Prevention [CDC] immunologic category 3) for an indefinite period until sustained immunologic recovery is observed. Pape et al. randomized adults with HIV who had completed a TMP-SMX treatment course for acute isosporiasis to one of three secondary prophylaxis regimens: TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) three times per week, sulfadoxine (500 mg) plus pyrimethamine (25 mg) once weekly, or placebo.<sup>16</sup> The active regimens in the two treatment arms were both effective in preventing recurrence of diarrhea during the observation period. However, the combination of sulfadoxine and pyrimethamine **is not recommended** in the United States because of increased risk of severe cutaneous reactions. In another study, adult patients with a clinical and microbiologic response to treatment of acute infection with TMP-SMX or ciprofloxacin received secondary prophylaxis for 10 weeks with the same agent used for treatment but at reduced doses: TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) three times per week. Both agents were effective in preventing recurrence during the monitoring period.<sup>17</sup> On the basis of these findings in adults, TMP-SMX, 2.5 mg/kg body weight twice daily of the trimethoprim component, administered 3 days per week,

either on three consecutive days (e.g., Monday, Tuesday, and Wednesday) OR on an alternating-day schedule (e.g., Monday, Wednesday, and Friday) is recommended for secondary prophylaxis in children with HIV. Patients intolerant of TMP-SMX may receive pyrimethamine (plus folinic acid) as secondary prophylaxis.<sup>18</sup> Ciprofloxacin three times weekly can also be considered as a second-line alternative.

### ***Discontinuing Secondary Prophylaxis***

There are no data to provide guidance regarding the optimal duration of secondary prophylaxis. All patients should be monitored for recurrence, and severely immunosuppressed patients may benefit from receiving secondary prophylaxis indefinitely. However, secondary prophylaxis probably can be discontinued in patients without evidence of active *I. belli* infection who demonstrate sustained recovery from severe immunosuppression. In adults, a CD4 count >200 cells/mm<sup>3</sup> for >6 months is recommended before discontinuing secondary prophylaxis. In children, a reasonable time to discontinue secondary prophylaxis would be after sustained improvement in CD4 count or CD4 percentage from CDC immunologic category 3 to 1 or 2.

## **Recommendations**

### ***Primary Prevention***

#### **I. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent initial episodes of isosporiasis (cystoisosporiasis)?**

- Careful hand washing and thorough washing of fruits and vegetables are recommended to prevent exposure. Travelers to isosporiasis-endemic areas should avoid untreated water for drinking, brushing teeth, and in ice, as well as unpeeled fruits and vegetables (**expert opinion**).

Because isosporiasis results from ingestion of sporulated oocysts, such as in contaminated food or water, careful handwashing and washing of fruits and vegetables are recommended.

### ***Treatment***

#### **II. In children with HIV infection, what are the best interventions (compared with no intervention) to treat isosporiasis (cystoisosporiasis)?**

- Trimethoprim-sulfamethoxazole (TMP-SMX) is recommended for treatment of isosporiasis in children with HIV infection (**strong, high**).

Three studies conducted among adults with HIV infection in Haiti demonstrated the efficacy of TMP-SMX for treatment for isosporiasis. In two of these studies, initial therapy with TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) 4 times daily for 10 days was effective in reducing diarrhea and abdominal pain.<sup>5,16</sup> In the third study, participants were randomized to receive either TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively) or ciprofloxacin (500 mg) twice daily for 7 days.<sup>17</sup> TMP-SMX treatment resulted in cessation of diarrhea in all 10 participants and negative results on stool examination at day 7 in 9 of the 10 participants, while ciprofloxacin resulted in resolution of diarrhea in 10 of 12 participants and negative stool examinations in 9 of the 12 participants. On the basis of these studies in adults, the recommended treatment for children with HIV infection is TMP-SMX, 5 mg/kg per dose of the trimethoprim component, given twice daily, for 10 days.

- Supportive care, including replenishment of fluids and electrolytes, should be provided (**expert opinion**).

There are no studies that address this specific management issue in isosporiasis. However, recognition and management of hydration status and electrolyte imbalance are key to management of infectious diarrhea.



## Secondary Prevention

### III. In children with HIV infection, what are the best interventions (compared with no intervention) to prevent recurrent episodes of isosporiasis (cystoisosporiasis)?

- Combination antiretroviral therapy (ART) administered to children with HIV infection to reverse or prevent severe immunodeficiency may be effective in preventing recurrence of isosporiasis (**weak, very low**).

In an observational study, the incidence of isosporiasis decreased after widespread availability of ART, except among persons with CD4 counts  $<50$  cells/mm<sup>3</sup>.<sup>15</sup> Although data in children are lacking, the relationship between severe immunosuppression and disease in adults suggests that initiation of ART in children with HIV infection may help prevent recurrence of isosporiasis.

- In children with severe immunosuppression, treatment of isosporiasis should be followed by secondary prophylaxis with TMP-SMX (**strong, high**).

Two randomized clinical trials among adults with HIV infection in Haiti demonstrated that secondary prophylaxis with TMP-SMX (160 mg and 800 mg of TMP and SMX, respectively, three times per week) following 10 days of initial treatment, was effective in preventing relapse during the monitoring period.<sup>16,17</sup> On the basis of these findings in adults, TMP-SMX, 2.5 mg/kg body weight twice daily of the trimethoprim component, administered 3 days per week, is recommended for secondary prophylaxis for children with HIV infection.

### IV. In children with HIV infection receiving secondary prophylaxis for isosporiasis (cystoisosporiasis), when can secondary prophylaxis be safely discontinued?

- Clinicians may consider discontinuing secondary prophylaxis in patients without evidence of active *Isospora* infection who have sustained improvement in immunologic status (CDC immunologic category 1 or 2) for longer than 6 months in response to ART (**weak, very low**).

There are no clinical trials demonstrating the optimal duration of secondary prophylaxis for isosporiasis. However, the observation that improved immunologic status associated with ART reduced the incidence of infection<sup>15</sup> and recommendations for other opportunistic infections suggest that secondary prophylaxis can be safely discontinued when sustained improvement in immunosuppression is demonstrated.

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### Dosing Recommendations for Prevention and Treatment of Isosporiasis (Cystoisosporiasis)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b>	There are no U.S. recommendations for primary prophylaxis of isosporiasis.	N/A	Initiation of ART to avoid severe immunodeficiency may reduce incidence; TMP-SMX prophylaxis may reduce incidence.
<b>Secondary Prophylaxis</b>	<u>If Severe Immunosuppression:</u> <ul style="list-style-type: none"><li>• TMP-SMX 2.5 mg/kg body weight of the TMP component (maximum 80 mg TMP) twice daily by mouth 3 times per week</li></ul>	Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid 5-15 mg by mouth once daily. <u>Second-Line Alternative:</u> <ul style="list-style-type: none"><li>• Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth 3 times per week</li></ul>	Consider discontinuing secondary prophylaxis in patients without evidence of active <i>Isospora</i> infection who have sustained improvement in immunologic status (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for >6 months in response to ART.  In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no data exist for dosing in children. Thus, the recommended dose for secondary prophylaxis in children is pyrimethamine 1 mg/kg (maximum 25 mg) by mouth once daily.  Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues.
<b>Treatment</b>	TMP-SMX 5 mg/kg body weight of the TMP component (maximum 160 mg TMP) twice daily by mouth for 10 days	Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid 5-15 mg by mouth once daily for 14 days <u>Second-Line Alternatives:</u> <ul style="list-style-type: none"><li>• Ciprofloxacin 10–20 mg/kg body weight (maximum 500 mg) by mouth twice daily for 7 days</li><li>• Nitazoxanide (see doses below) for 3 consecutive days</li></ul> <u>Children Aged 1 Year–3 Years:</u> <ul style="list-style-type: none"><li>• Nitazoxanide 100 mg by mouth every 12 hours</li></ul> <u>Children Aged 4 Years–11 Years:</u> <ul style="list-style-type: none"><li>• Nitazoxanide 200 mg by mouth every 12 hours</li></ul> <u>Adolescents Aged ≥12 Years and Adults:</u> <ul style="list-style-type: none"><li>• Nitazoxanide 500 mg by mouth every 12 hours</li></ul>	If symptoms worsen or persist, the TMP-SMX dose (5 mg/kg/dose of the TMP component) may be given more frequently (e.g., 3–4 times daily by mouth for 10 days) and/or the duration of treatment may be increased to 3–4 weeks.  The optimal duration of treatment with pyrimethamine has not been established.  Ciprofloxacin is not a drug of choice in children because of increased incidence of adverse events, including events related to joints and/or surrounding tissues.

**Key to Acronyms:** CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; ART = antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole